Invincible arrogance—and patients suffer

"Mainstream programmes . . . have no less of an obligation to get their facts right, to give both sides of any controversy, and to consider the effect they may have on hapless patients caught up in whatever is the area of concern."

So wrote Sir Michael Swann, then chairman of the BBC, in a letter to the BMJ in 1978 in which he accepted that the severe criticisms made by doctors of the Panorama programme on ECT had been justified. In an attempt to respond to Sir Michael’s conciliatory approach and to try to improve the relations between the medical profession and television journalists we began publication of regular reviews of medical programmes. “Medicine and the Media” has found much to praise in its first two years. On 13 October, however, Panorama re-entered medicine with a programme on brain death that we described as a disgrace. Nearly two months have now elapsed; but this time there has been no hint of an apology—not any word of regret for the damage and distress caused to patients waiting for a kidney transplant. Indeed, on 22 November Mr David Dimbleby told Panorama viewers that, “we stand by our programme.”

Does Panorama stand by the advance publicity in the Radio Times for 11-17 October, with its tasteless cartoon picturing a transplant unit beneath a cinema hoarding for “The Premature Burial” and “The Night of the Living Dead,” and its assertion that “transplant surgeons have got their colleagues in a fix because they’ve put them under pressure to diagnose death in the potential donor sooner than they want to?” Does Panorama stand by its claim that the North American patients it pictured had been declared dead by “doctors applying the British criteria?” Both these allegations have been shown to be patently false in the correspondence after the programme. Presumably Mr Dimbleby has not read the letters in the national press and in the BMJ and Lancet—in which case his loyalty to his staff is alarmingly blinkered, for otherwise his assertion is both obdurate and unreasonable.

In their defence the Panorama team have argued that they brought into the open a medical controversy. In fact, two issues have been debated, neither of which had been in contention before 13 October. Firstly, the programme claimed—and one of its participants, Dr Ronald Paul, has since argued at length—that the diagnosis of brain death would be strengthened by a requirement for an electroencephalogram. The flaws in that proposal have been exposed by Dr Pamela Prior, and by Dr Bruce Macgillivray at the press conference arranged last week by the BMA and the Conference of Royal Colleges and their Faculties. Secondly, British authorities on brain death were said not to have validated their criteria—they were, said Panorama, operating a “self-fulfilling prophecy” by certifying death and then switching off the ventilator. In fact, as Professor Bryan Jennett explained at the press conference, and would have liked to have told viewers on the programme, in 25-50% of patients the ventilator is not switched off after brain death is certified—because the relatives ask for ventilation to be continued. Each year several hundred such patients continue on life support until their hearts stop. Not one has recovered—and had such a recovery occurred, should we not have heard of it in the last few weeks? British neurologists had assessed some 4000 such patients to the point where the heart stopped beating before the criteria on brain death were agreed in 1976.

The weight and complexity of the evidence against Panorama became clear last week at the press conference. The explanation by the medical experts took 20 minutes; after 40 minutes’ questioning some of the journalists present still found some of the concepts difficult. As Professor Gordon Robson observed, the five minutes offered by Panorama for a medical reply was plainly absurd. Brain death is a complex issue; even one hour is scarcely long enough for an explanation to a medical, let alone non-medical audience. Mr Richard Lindley, the Panorama reporter, and Ms Anne Moir, the producer, betrayed their own lack of understanding of the physiological background by their absurd assertion in a letter to the Sunday Times that every patient on a ventilator has a malfunctioning brain stem.

Our continuing attack on Panorama is justified by the fact that the losers in this confrontation are patients. In the first four weeks after the brain-death programme the numbers of kidney donors fell from the 50 in September to only 28, which means that some patients whose lives could have been saved by dialysis have died. Television journalists sometimes ask why medicine claims that it should have special treatment. The answer lies in the damage that may result from a programme that causes unnecessary fears or misconceptions. Despite many excellent medical programmes, in the last decade television has discouraged parents from getting their children immunised against whooping cough; suggested that interferon could cure advanced cancer; and portrayed ECT and psychosurgery as dangerous and ineffective.

Two years’ experience with “Medicine and the Media” has shown that doctors enjoy most medical programmes and
Calmodulin

Calmodulin seems to be unique among the calcium-binding proteins for its widespread distribution and multiplicity of functions; indeed, the unravelling of its story has been claimed as one of the major scientific achievements of the 1970s. Over 30 years ago Hellman and Wieland observed that the injection of a small quantity of ionic calcium into a muscle fibre caused it to contract. Intracellular calcium ion concentrations are normally some 10,000 times lower than those observed outside the cell. Stimulation of the cell, however, may cause the intracellular concentration of ionised calcium to rise above 100 nmol/l (0·4 µg/ml). At these concentrations intracellular proteins such as calmodulin and troponin C (found in skeletal muscle) bind calcium ions and undergo a change in conformation. Thus activated, the complex of binding protein and calcium interacts with a receptor protein, which in turn controls one of several biochemical pathways. This system offers a striking parallel to the cyclic adenosine monophosphate (AMP) system, in which a regulatory protein is activated by binding cyclic AMP to form a complex that in turn phosphorylates and thus activates dependent regulatory proteins.

The calmodulin and cyclic AMP systems seem to be closely interlinked, for activated calmodulin activates the phosphodiesterase that breaks down cyclic AMP and cyclic guanosine monophosphate. Additionally, and somewhat perplexingly, calmodulin also activates the enzyme adenylyl cyclase, at least in the brain and adrenals, so increasing concentrations of cyclic AMP. A further function of calmodulin is the coupling of excitation and contraction in smooth muscle (a task performed by troponin C in striated muscle). Calmodulin is now thought to activate the enzyme that transfers a phosphate residue to a myosin light chain, thus promoting the interaction of actin and myosin. It may also help to supply the energy needed for this process, since it appears to be a constituent of phosphorylase kinase, the enzyme that activates the glycogendehydrolysing enzyme phosphorylase. A third probable function of calmodulin in muscle is promoting the subsequent efflux of calcium from the cell (and hence muscle relaxation) by stimulating the calcium pump.

In nerve cells calmodulin appears to play an important part in promoting the phosphorylation of various proteins, and it may be concerned in the control of the synthesis and release of neurotransmitters. Several familiar drugs interact with these processes. Phentoin, for example, blocks in vitro the phosphorylation of nerve terminal proteins and the release of noradrenaline normally promoted by calcium ions. Trifluoperazine, a phenothiazine tranquiliser, avidly binds and inactivates calmodulin. Furthermore, mammalian brain contains several proteins of undetermined function that bind calmodulin.

Other important functions of calmodulin include the assembly and disassembly of microtubules during cell division and (in all probability) the regulation of endoperoxidase and thromboxane A2 in platelets. Regulation of calmodulin itself appears to be through the regulation of fluxes of calcium ions rather than through the alteration of its rates of synthesis or breakdown. The structure of calmodulin has been highly conserved through evolution: four binding sites for calcium ions are found in all calmodulins, and even those from widely divergent species have closely similar amino-acid sequences. Its biological activity seems to depend on the integrity of the entire molecular structure.

Mutations that lead to the loss of the biological potency of calmodulin are likely to be lethal in view of its importance in the regulation of many fundamental biological functions. So its practical importance for clinicians is most likely to come from greater understanding of the actions of current drugs and a more enlightened search for better ones. Already vast efforts in clinical and laboratory research are being directed to such topics as psychotropic drugs, drugs that impede the inflow of calcium into the myocardium after contraction, agents that reduce platelet stickiness, and antiinflammatory treatment. Know-